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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/678,202	BAR-OR ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/26/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,28-31 and 375-381* is/are pending in the application.

4a) Of the above claim(s) *12-20,25,26 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 21-24, 28-30, 375-381* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 11/26/04, claim 1 has been amended. Claims 1-26, 28-31 and 375-381 remain pending. Claims 12-20, 25-26, 31 remain withdrawn from consideration.

Claims 1-11, 21-24, 28-30, 375-381 are examined in this Office action.

Applicants' arguments filed 11/26/04 have been considered and found persuasive in part.

- The ODP (obviousness double patenting) rejections are withdrawn.
- The rejection over Blaschuk ('821) in view of Malins or Knight is withdrawn.
- The rejection of claims 1, 9, 10, 21-24, 28-30, 375-381 over Deghenghi (USP '548) is withdrawn.

. . .

The abbreviation **ROS** hereinbelow refers to *reactive oxygen species.*

The abbreviation **AD** hereinbelow refers to *Alzheimer's Disease.*

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 now recites that the peptide (represented as P_1-P_2) "binds a metal ion... with the result that the damage done by the ROS is reduced". However, this is not fully supported by the specification as filed. The passage on page 13, line 19+ of the specification is noted. At this location it is asserted that peptide fragment P_1 binds ions of those transition metals that are present in Groups Ib, IIb, IIIb, IVb, Vb, VIb, VIIb and VIII of the periodic table. However, claim 1 implies that the peptides (represented as P_1-P_2) will bind to <u>any</u> metal ion, transition metal or not. Ions of metals such as Na, K, Rb, Cs, Ca Sr, W, Zr, and Hf would be included within the scope of those that are now asserted to bind to peptide P_1-P_2 (in claim 1). Ions of metals that occur within the lanthanide and actinide series would be included also. This is new matter in and of itself. In addition, the claim implies that damage done by ROS will be reduced <u>as a consequence of</u> such binding. It is not evident, however, how or why damage done by ROS would be reduced as a consequence of binding to ions of metals such as Na, K, and Ca. Nor is it clear which metals applicants believe are present in the animal to begin with. Do the peptides (to which the claims are drawn) bind indium, thallium

gallium, geranium, arsenic and polonium in humans, and is the "damage" caused by ROS mitigated as a consequence?

✧

Claims 1-11, 21-24, 28-30, 375-381 rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that the following two peptides can inhibit cuprous ion-catalyzed production of hydroxyl radicals:

DAHK

DAHKSEVAHRFK

(Note that SEQ ID NOS: 4-6 fall outside the scope of the claimed invention).

Even if the peptides (to which the claims are drawn) could contain no more and no less than 11 amino acids, and if all of the amino acids had to be genetically encoded, there would still be more than 10 **trillion** peptides encompassed. And if the peptides (to which the claims are drawn) could contain no more and no less than 101 amino acids, and if all of the amino acids had to be genetically encoded, there would still be more than 10^{130} peptides encompassed, or the following quantity:

10,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,
000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,00
0,000,000,000,000,000,000

Of course, the actual number of peptides encompassed is vastly greater, since all of the 100-mers, 99-mers, 98-mers, etc. are encompassed as well, and moreover, the peptides are not limited to genetically encoded amino acids.

Thus, applicants are extrapolating, first, from the results obtained with just two peptides, to a property of an infinite number of peptides. On top of this, applicants are extrapolating from the results obtained with just one metal ion, to <u>any</u> metal ion in the periodic table. Clearly then, the claimed invention is unduly broad in view of the enabling disclosure.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Consider the following:

- Coddington, A. (*Biochimica et Biophysica Acta* **44**, 361-3, 1960) discloses (page 362) that acetylated albumin does not bind iron in the pH range 3.8 to 7.4, whereas the native albumin does. This reference supports the proposition that minor

structural changes in a peptide can have significant effects on metal-binding capability.

- Mack (*J. Am. Chem. Soc.* **110**, 7572, 1988) discloses that a peptide bearing the sequence Gly-Gly-His at the N-terminus failed to reduce the damage (to DNA) that is caused by reactive oxygen species.

- Guan, Le Luo (*Biochemical and Biophysical Research Communications* 283(4), 976-981, 2001) discloses that a peptide isolated from a marine sponge binds Fe(III) and Cr(III), but does not bind Cu, Zn, Co, Ni, Al or Ti cations.

- Kiyokawa, T. (*Journal of Peptide Research* **63**(4), 347-353, 2004) discloses that a minor structural change eliminated the propensity of a peptide to bind nickel.

- Chen, Hua-Ming (*Journal of Agricultural and Food Chemistry* **46**(1), 49-53, 1998) discloses that the metal ion chelating propensity of peptides does not correlate with their capacity to inhibit ROS formation.

With few exceptions, none of the peptides disclosed in the foregoing references is included within the scope of the instant claims. The point is, however, that if a given peptide does bind one or more metal ions, one cannot predict, merely by viewing the structure of the peptide, which metal ions it will bind, and which it will not.

A related issue is that, as applicants are no doubt aware, peptides and proteins do not exist in solution merely as linear entities. Rather, they form globular structures; i.e., the peptides and proteins fold into a tertiary structure, in which there are hydrophobic regions and hydrophilic regions. For example, suppose that the N-terminus of a given 100-mer polypeptide were the following:

Leu-Phe-His-Tyr-Val-Trp

As applicants may be aware, when a given side chain of an amino acid is present in a hydrophobic "pocket", its properties can be substantially altered. For example, a pKa of a glutamic acid side chain could easily be as high as 10 when present in a hydrophobic pocket. The pKa (of the conjugate acid) of a histidine acid side chain (i.e., imidazole) could easily be as low as 2 in such a circumstance. Metal ion binding propensities can similarly be perturbed. Certainly, for the case in which the N-terminal region of the peptide is hydrophobic, and where the peptide has more than about 20 amino acids, one cannot "predict" metal binding propensities, because of tertiary structure effects.

Accordingly, the skilled peptide chemist cannot predict what the effects of varying amino acid sequence and composition will be on metal binding capability; in addition, one cannot predict what the effects will be of adding 80 or more amino acids to the C-terminus of the peptides that have been tested.

In addition, applicants have pointed to Hahn (USP 4,816,449) as providing evidence that the claimed peptides will stimulate NK cell cytotoxicity. In particular, applicants have argued that the following peptide, which falls within the scope of instant claim 1, is effective to augment NK cell cytotoxicity: Ala-Arg-His-Ser. As is well known in the art, NK cells produce significant quantities of ROS. Thus, the skilled artisan would conclude that peptides falling within the scope of claim 1 will actually increase the level of damage caused

by ROS, rather than decrease it.

In accordance with the foregoing, "undue experimentation" would be required to synthesize even 1/10 of the peptides (to which the claims are drawn). "Undue experimentation" would be also be required to determine which of the (infinite array of) peptides will bind metal ions and whether the binding does indeed result in decreased production of ROS.

✧

Claims 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of claims 21-24, 28-30, 375-381 is dependent on a non-elected claim.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability

of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. 103 as being unpatentable over Deghenghi (USP 5,932,548) in view of Zweier, J. (*Proc Natl Acad Sci* 84: 1404-1407, 1987) or O'Neill C. A. (*American Journal of Physiology*, (1996 Aug) 271 (2 Pt 2) H660-7) or Bolli R. (*Journal of Clinical Investigation*, (1995 Aug) 96 (2) 1066-84) or Flaherty, J. T. (*Am. J. Med.* 91, 3C79S-3C85S, 1991) or Cai Q. (*Journal of Cardiovascular Pharmacology*, (1995 Jan) 25 (1)) or Giannitsis E. (*Pacing and clinical electrophysiology* : PACE, (1998 Jan) 21 (1 Pt 2) 157-62) or Lonn E. (*Canadian journal of cardiology*, (1994 Mar) 10 (2) 203-13).

As indicated previously, Deghenghi discloses (col 4, line 10) the following peptide:

Tyr-Ala-His-D-Mrp-Ala-Trp-D-Phe-Lys-NH_2

Also disclosed is that this is one of several peptides that is useful for treatment of myocardial ischemia. Accordingly, whatever damage is caused by ROS (or any other molecular entities) in the manifestations of ischemia will be mitigated. Deghenghi does not disclose that the damage that occurs in ischemia is mediated by ROS. Each of the secondary refereces, however, discloses that the damage that occurs in ischemia is mediated by ROS.

In response to the rejection over Deghenghi taken by itself, applicants have argued that in order for this ground of rejection to be proper, the reference (or at least a secondary reference) must disclose that the peptide in question "binds a metal ion". However, this

property of binding metal ions is a property of the peptide, since the structure of a compound and its properties are inseparable. As applicants have observed, any peptide which contains a histidine which is three amino acids from the N-terminus will bind a metal ion. Thus, the Deghenghi peptide has the property of binding metal ions [(*Ex parte Novitski* (26 USPQ2d 1389, 1993); *Bristol-Myers Squibb v. Ben Venue Laboratories* (58 USPQ2d 1508, 2001); *In re May and Eddy* (197 USPQ 601)].

Thus, the claims are rendered obvious.

✧

Claims 1, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Rosenzweig (WO 00/23469).

Rosenzweig discloses (page 26, line 21) a method of treating ischemic injury by administering any of several peptides. Among those are the peptides designated SEQ ID NO: 6, 15, 16, 29-34 and 37, all of which have a histidine at the requisite position.

Thus, the artisan of ordinary skill would reason that if the peptides are effective to treat ischemic injury, then it will necessarily be true that the "damage" which gave rise to the ischemic injury is mitigated as well.

Thus, the claims are rendered obvious.

✧

Claims 1, 3, 9, 21-24, 28-30 are rejected under 35 U.S.C. §103 as being unpatentable over

Liotta (USP 5,270,447) in view of Malins (*Proc. Natl. Acad Sci.* **93**, 2557, 1996); or Liotta in view of Knight (*Ann Clin Lab Sci* **25**, 111, 1995); or Malins in view of Liotta, or Knight in view of Liotta.

As indicated previously, Liotta discloses (figure 6; col 5, line 3; table I, cols 5-6) the following peptide:

AA**H**EEICTTNEGVM

Also disclosed (e.g., col 15, line 56+) is that the peptide can be used to treat cancer.

Liotta does not disclose that tumor cell growth is caused by reactive oxygen species. Malins and Knight both disclose that tumor cell growth is caused at least in part by reactive oxygen species. Neither of Malins and Knight discloses a peptide falling with the scope of instant claim 1. One of ordinary skill would expect that if cancer is caused by ROS, or if tumor cells give rise to ROS (or if both is true), then eliminating (at least in part) the tumor cells can only take place if the damage caused by the ROS has been mitigated. It may be the case that Liotta does not teach that the disclosed peptides act to directly reduce the formation of ROS. However, given that tumor cells increase the level of ROS, it follows therefrom that if the population of tumor cells is reduced, the amount of ROS produced by the tumor cells will be reduced as well. If the amount of ROS that is produced declines, then it stands to reason that the "damage" caused by those ROS's will also decline.

In response to the foregoing, applicants have argued that (a) the examiner has not provided

an adequate reason for combining references and (b) none of the references discloses that the peptide in question will bind metal ions.

The first point is that it is appropriate to consider the claims in light of the specification. The specification discloses (e.g., page 32, line 24+) that one of the objectives of administering the peptides is to treat cancer. Thus, the artisan of ordinary skill would have sought out a reference such as Liotta for a method of treating cancer. The artisan of ordinary skill would have then sought out a reference such as Malins or Knight to provide evidence that reduction of ROS had been achieved by eradication of the cancer. None of the references disclose the metal-binding property of the peptide, but the peptide has this property, given its structure.

. . . .

There is an alternative explanation to the foregoing, which is the following. The artisan of ordinary skill would reason that if one can succeed in mitigating the formation of ROS, it will follow that "damage" resulting from production of ROS will be mitigated as well. The claims impose no limitations of any kind on the nature of the damage. It would include damage to cell membranes, damage to membrane-bound proteins, damage to intracellular or extracellular proteins, damage to DNA, and generally damage to tissue of any kind. Thus, the artisan of ordinary skill would have been motivated to eliminate any source of the ROS. As such, the artisan of ordinary skill would have had motivation to seek out sources

of ROS in the mammalian body. The artisan of ordinary skill would have sought references such as Malins and Knight which provide information on sources of ROS. The artisan of ordinary skill would reason that by eliminating the cancer (by the Liotta procedure), he would succeed in eliminating one source of ROS. As for the metal-binding capability, this is determined by the structure of the peptide; the peptide has the property in question. [(*Ex parte Novitski* (26 USPQ2d 1389, 1993); *Bristol-Myers Squibb v. Ben Venue Laboratories* (58 USPQ2d 1508, 2001); *In re May and Eddy* (197 USPQ 601)].

The rejection is maintained.

✧

Claims 1, 3, 9, 21-24, 28-30 are rejected under 35 U.S.C. §103 as being unpatentable over Liotta (USP 5,270,447) in view of Malins (*Proc. Natl. Acad Sci.* **93**, 2557, 1996); or Liotta in view of Knight (*Ann Clin Lab Sci* **25**, 111, 1995) further in view of Zachariou (*Journal of Protein Chemistry* **14**(6), 419-30, 1995).

As indicated previously, Liotta discloses (figure 6; col 5, line 3; table I, cols 5-6) the following peptide:

AAHEEICTTNEGVM

Also disclosed (e.g., col 15, line 56+) is that the peptide can be used to treat cancer.

Liotta does not disclose that tumor cell growth is caused by reactive oxygen species.

Malins and Knight both disclose that tumor cell growth is caused at least in part by reactive oxygen species. Neither of Malins and Knight discloses a peptide falling with the scope of instant claim 1.

Zachariou discloses that peptides which contain aspartic acid or glutamic acid tend to exhibit some affinity for metal ions such as copper and iron. Zachariou does not disclose the peptides to which the claims are drawn.

The explanation given above (Liotta in view of Malins or Knight) applies here as well, but with the addition that the peptide chemist of ordinary skill would have expected (in view of Zachariou) that the Liotta peptide will exhibit some affinity for metal ions such as copper and iron owing to the presence of the glutamic acid residues in the peptide.

Thus, the claims are rendered obvious.

✧

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Konishi (USP 4,461,724) in view of Ben-Hamida (*Inflammation research : Official Journal of the European Histamine Research Society* **47** (4) 193-9, 1998) or Danielsson D (*Digestive diseases and Sciences* **43** (9 Suppl) 167S-173S, 1998) or Iinuma S (*Digestive Diseases and Sciences* **43** (8) 1657-64, 1998) or Manjari V (*Prostaglandins, leukotrienes, and Essential Fatty Acids* **59** (6) 401-6, 1998).

As indicated previously, Konishi discloses the use of peptides for treating ulcers. The

peptides contain a histidine residue which is located 3 amino acids from the N-terminus, as required of the instant claims. Konishi does not disclose that the symptoms of ulcers are mediated by "ROS". Each of Ben-Hamida, Danielsson, Iinuma, Manjari disclose that ulcers are mediated by "ROS".

In response to the foregoing, applicants have dismissed the disclosure of Danielsson by arguing that pathogenesis of *H. pylori*- associated gastroduodenal disease is not well understood. However, as admitted by applicants, Danielsson does provide an affirmative disclosure that *H. pylori* induces formation of ROS in persons with peptic ulcers. Ben-Hamida similarly discloses that *H. pylori* induces formation of ROS in persons with ulcers. Applicants have made no statement contradicting this conclusion. Manjari discloses a similar conclusion. Again applicants have made no assertion that *H. pylori* fails to induce formation of ROS in persons with ulcers.

It appears that applicants are attempting to minimize the fact of ROS formation (in ulcer patients) by arguing that other factors are involved. The examiner actually agrees with applicants that the etiology and symptoms of ulcers cannot be explained simply by the formation of ROS. But even if it were true that 90% of the "damage" in ulcer patients is caused by factors other than ROS, this would not undermine the validity of this rejection. The claims require only that some degree of "damage" be reduced, not that the damage is reduced to the point that a therapeutic benefit is achieved.

As indicated, Konishi does not teach that the anti-ulcer effect derives directly from inhibiting the production of ROS. However, each of the secondary references discloses that the presence of *Helicobacter* gives rise (directly or indirectly) to production of ROS. Thus, perhaps the peptides of Konishi are acting by sequestering metal ions, leading to decreased ROS production. Or perhaps the peptides of Konishi inhibit one of the cellular processes of *Helicobacter*, leading to decreased proliferation of the bacteria which in turn leads to decreased production of ROS. Or perhaps the peptides act by inhibiting neutrophil oxidase. Or perhaps the peptides do not actually inhibit the production of ROS, but instead accelerate healing of the affected tissues. Regardless of which of these mechanisms may be acting, the result is that the "damage" caused by the ROS will be mitigated if the peptides are in fact effective to successfully treat patients afflicted with ulcers.

Thus, the claims are rendered obvious.

✧

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Ben-Hamida (*Inflammation research : Official Journal of the European Histamine Research Society* **47** (4) 193-9, 1998) or Danielsson D (*Digestive diseases and Sciences* **43** (9 Suppl) 167S-173S, 1998) or Iinuma S (*Digestive Diseases and Sciences* **43** (8)

1657-64, 1998) or Manjari V (*Prostaglandins, leukotrienes, and Essential Fatty Acids* **59** (6) 401-6, 1998) in view of Konishi (USP 4,461,724).

The teachings of the references were indicated previously. This ground of rejection is the reverse of that above, i.e., rather than rejecting over Konishi in view of Ben-Hamida, Danielsson, Iinuma, or Manjari, it is based on Ben-Hamida, Danielsson, Iinuma, or Manjari in view of Konishi.

This ground of rejection approaches the question of obviousness from the perspective of one who has determined (from Ben-Hamida, Danielsson, Iinuma, and Manjari) that *H. pylori* produces ROS, and that ROS are harmful. The artisan of ordinary skill would have been motivated to mitigate the initial damage caused by ROS, or in the alternative, to reverse the damage that has been caused by the ROS. Applicants may choose to argue that mitigating the initial damage caused by ROS is not the same as reversing the damage after it has occurred. Yet it is unlikely that applicants will be able to devise a biochemical or histological assay to distinguish these two possibilities.

Thus, the claims are rendered obvious.

✧

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. 103 as being unpatentable over Hagiwara (JP 62-116565) in view of Ben-Hamida (*Inflammation research : Official Journal of the European Histamine Research Society* **47** (4) 193-9, 1998) or Danielsson D

(*Digestive diseases and Sciences* **43** (9 Suppl) 167S-173S, 1998) or Iinuma S (*Digestive Diseases and Sciences* **43** (8) 1657-64, 1998) or Manjari V (*Prostaglandins, leukotrienes, and Essential Fatty Acids* **59** (6) 401-6, 1998)

Hagiwara discloses that the tetrapeptide A-D-H-K can be used to treat ulcers. Hagiwara does not disclose that the symptoms of ulcers are mediated by "ROS". Each of Ben-Hamida, Danielsson, Iinuma, Manjari disclose that ulcers are mediated by "ROS".

Thus, the claims are rendered obvious.

✧

Claims 1, 4, 9-11, 21-24, 28-30 are rejected under 35 U.S.C. §103 as being unpatentable over Hahn (USP 4,816,449) in view of Gaffar (USP 4,975,423).

Hahn discloses (col 15, table 2) that the following peptide inhibits NK cell-induced cytotoxicity: Ala-Arg-His-Ser

Hahn does not disclose that NK cells produce ROS.

Gaffar discloses (col 1, line 30+) that NK cells cause "damage" by producing reactive oxygen species. Gaffar does not disclose any peptide falling within the scope of claim 1.

Thus, it would have been obvious to one of ordinary skill that by contacting the tetrapeptide A-R-H-S with NK cells, the amount of ROS produced will be reduced, and hence the "damage" caused by the ROS will be reduced also.

In response to the foregoing, applicants have argued that, while it may be true that the peptide in question will inhibit ROS production following binding to certain Fc receptors, there may exist certain other (unspecified) Fc receptors such that following binding, ROS production is *increased*. However, applicants have not identified the conditions under which any such increase will occur. Further, the claims do not specify what sort of damage is ostensibly being reduced, or what type of tissues might be affected. If a peptide is effective to reduce some kind of damage, in some type of tissue, under a given set of circumstances, then the requirements of the claims are met. The reference clearly sets forth conditions under which inhibition of ROS occurs. As applicants will be quick to agree, if a given phenomenon is observed in a "test tube" or "petri dish", the skilled artisan can confidently predict that the same phenomenon will occur in the intact animal.

Applicants have also argued that NK cells exhibit at least one activity in addition to its propensity to produce ROS. The examiner does not dispute this particular point. However, there is no evidence of record that NK cells fail to produce ROS. Whether NK cells exhibit one activity in addition to this, or 500 such activities, the fact remains that NK cells produce ROS, and that the peptide in question reduces formation of ROS.

✧

Claims 1, 4, 9-11, 21-24, 28-30 are rejected under 35 U.S.C. §103 as being

unpatentable over Hahn (USP USP 4628045) in view of Gaffar (USP 4,975,423).

Hahn discloses (table 5, col 23) that the following peptide inhibits NK cell induced cytotoxicity: Ala-Arg-His-Ser

Hahn does not disclose that NK cells produce ROS.

Gaffar discloses (col 1, line 30+) that NK cells cause "damage" by producing reactive oxygen species. Gaffar does not disclose any peptide falling within the scope of claim 1.

Thus, it would have been obvious to one of ordinary skill that by contacting the tetrapeptide A-R-H-S with NK cells, the amount of ROS produced will be reduced, and hence the "damage" caused by the ROS will be reduced also.

Claims 1, 4, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Heavner (WO 94/14836).

Heavner discloses (p. 26, line 21 and page 46, line 19) various peptides for treating ischemia. Among them is SEQ ID NO: 21, which is the following: SKHKLALCY (see, e.g., page 10, line 32; page 24, line 25).

The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of the ischemia.

Thus, the claims are rendered obvious.

✧

Claims 1, 4, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Heavner (WO 94/14836) in view of Moyle (USP 5,919,900) or Nierman (USP 5,529,907) or Serhan (USP 6,008,205).

Heavner discloses (p. 26, line 21 and page 46, line 19) various peptides for treating ischemia. Among them is SEQ ID NO: 21, which is the following: SKHKLALCY (see, e.g., page 10, line 32; page 24, line 25). It is also disclosed that the peptides inhibit binding of neutrophils to P-selectin. In the "backround" section of Heavner, it is disclosed that compounds acting by the same mechanism as the disclosed peptides inhibit the binding of neutrophils to endothelium. Heavner does not disclose that neutrophils produce ROS. Each of Moyle, Nierman and Serhan disclose that neutrophils produce ROS. (See, e.g., col 1, line 34+ Serhan; col 2, line 65+ of Nierman; and several locations of Moyle such as col 1, line 45+ and col 2, line 60).

One of ordinary skill in possession of the references would determine that the peptides of Heavner will reduce the recruitment of neutrophils to the site of injury, and hence the "damage" caused by the neutrophils at that site will be reduced.

Thus, the claims are rendered obvious.

✧

Claims 1, 9, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Saitoh (WO 94/09808).

Saitoh discloses various peptides for treating neurological disease, or ischemia (e.g., col 6, line 21). Among the peptides asserted to be effective in this regard is the peptide designated SEQ ID NO: 8 (see page 18 and page 40). The sequence of this peptide is the following: AK**H**RERMSQVM

The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of the ischemia.

Thus, the claims are rendered obvious.

✧

Claims 1, 9, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Saitoh (WO 94/09808) in view of Hensley (*Ann N. Y. Acad. Sci.* 786:120-134, 1996); or Hensley in view of Saitoh.

As indicated previously, Saitoh discloses various peptides for treating neurological disease such as Alzheimer's. Among the peptides asserted to be effective in this regard is the peptide designated SEQ ID NO: 8 (see page 18 and page 40). The sequence of this peptide is the following:

AK**H**RERMSQVM

Saitoh does not disclose that AD mediated by ROS. However, Hensley discloses that AD is mediated by ROS. Thus, the artisan of ordinary skill would reason that if a compound is effective to treat AD, then the compound is also effective to reduce the "damage" that is caused in patients afflicted with the disorder.

In response to the foregoing, applicants have argued that the rejection is inadequate because the examiner has not provided motivation to combine references. The examiner will acknowledge that the neurologist of ordinary skill could endeavor to treat AD (in accordance with the Saitoh invention) without the need to consult the Hensley reference. However, there is more to the analysis. The first point is that it is appropriate to consider the claims in light of the specification. The specification asserts (e.g., page 32+) that by reducing the damage caused by ROS, one can provide therapeutic benefit to patients afflicted with such diseases. Among the diseases referred to is AD (page 33, line 2). So the question is not simply whether the artisan of ordinary skill would have been motivated to reduce damage done by ROS; an alternative question would be whether the artisan of ordinary skill would have been motivated to reduce damage done by ROS in the hope of providing benefit to the patient afflicted with AD. Given the objective of treating AD (which has been fully endorsed by the instant specification), one can "extract out" from (instant) claim 1 an embodiment which is relevant to this rejection; this illustrated by claims 1000-1001

below:

1000. A method of treating AD (Alzheimer's Disease) comprising administering to a patient the following peptide

AKHRERMSQVM

wherein said method, the peptide reduces the damage to at least one tissue that would otherwise occur in AD.

1001. The method according to claim 1000, wherein said damage is caused, at least in part, by ROS.

These claims (1000-1001) do not constitute an exact subgenus of claim 1; however, they do constitute a subgenus that would be obtained if one combined the explicit language of claim 1 with the ultimate objective of claim 1. Given these claims, it becomes more clear what the purpose of combining references would be. But consider first the following simple claim:

1002. A method of treating a headache comprising the step of administering aspirin to a patient in combination with a liquid that exhibits the following properties: (a) it exhibits hydrogen bonding capability, (b) it freezes at 0 °C when subject to a pressure of one atmosphere, and (c) it boils at 100 °C when subject to a pressure of one atmosphere.

Suppose that an examiner rejected this claim over a "first" reference that discloses a method of treating a headache by administering aspirin, and a "second" reference that discloses that water boils at 100 °C and freezes at 0 °C. Would applicants argue that

the examiner had failed to provide motivation to combine references? Clearly, it does not take a board certified neurologist working together with a PhD in physical chemistry to know that an aspirin tablet, taken with a glass of water, can often be effective to treat a headache. But according to applicants' arguments, this claim (claim 1002) would not have been obvious, even with all of the necessary references, unless an examiner could come up with a reason as to why a person suffering from a headache would want to go to a library and seek out chemical literature on the physical properties of water. The examiner would maintain that in the case of claim 1002, the question would not be whether a person suffering from a headache would want to seek out journal articles on the properties of water, but rather, the question would be whether the requirements of the claims had been met having already determined that providing both aspirin and water is obvious in view of the prior art.

Now consider again claims 1000 and 1001. As indicated, if one combines the language of claim 1 with the intent of claim 1, one comes up with the objective of treating AD (among other diseases). The first question then is, would it have been obvious to treat AD using a peptide in which a histidine is present three amino acids from the N-terminus? Clearly the answer is in the affirmative. The next question is whether the artisan of ordinary skill (e.g., a neurologist) would have expected that the peptide would reduce the damage to at least one tissue that would otherwise

occur in AD, and in particular the damage that is caused by ROS. This is where the discussion above comes into play.

The artisan of ordinary skill does not have to know why or how the peptide "works", as long as it is effective to treat the disease. But in endeavoring to determine whether the peptide is also effective to mitigate damage caused by ROS, the skilled artisan would have been motivated to seek out a reference which answers this question. In the aspirin case above, novelty does not accrue to a claim that is drawn to a method of treating a headache merely because convoluted language is chosen so as to force an examiner to find a reference on the physical properties of water. Similarly, novelty does not accrue to a claim that is drawn to a method of treating AD, merely because it attempts to force an examiner to find a reference on one of the underlying biochemical mechanisms of the disease. As it happens, the Hensley reference provides the necessary information. With respect to this reference, there are two separate and distinct arguments. The first argument is that what is obvious is that the net effect of using the Saitoh peptide would be to reduce the damage done by ROS, not (necessarily) by limiting the quantity of ROS formed, but rather, by repairing tissue that had been damaged by ROS. That is, suppose applicants were presented with two rats, both of which had been subject to some sort of oxidative stress. The "first" rat is administered a "first" peptide, and the "second" rat is administered a "second" peptide.

The first peptide acts by limiting the initial formation of ROS, and hence limits the "damage" to tissue which is caused by the ROS. The second peptide has no effect on the formation of ROS, but is instead effective to repair the damage which was caused by ROS. Suppose that applicants were presented with two rats, both of which had been subject to oxidative stress, and one of which had been administered the first peptide, and to the other the second peptide (as explained above). If the two rats were indistinguishable by any biochemical or histological test, how would applicants go about determining which rat had been administered the first peptide, and which rat had been administered the second peptide? If applicants are unable to determine which is which, how can applicants then argue that the artisan of ordinary skill could make such a determination? There is a second argument with respect to the Hensley reference, which is commingled with the issue of metal binding. It is acknowledged that neither reference (Saito or Hensley) discloses that the peptide will bind metal ions. But because of its structure, the peptide will bind metal ions. This is not simply a scientific question, but a legal one as well. [(*Ex parte Novitski* (26 USPQ2d 1389, 1993); *Bristol-Myers Squibb v. Ben Venue Laboratories* (58 USPQ2d 1508, 2001); *In re May and Eddy* (197 USPQ 601)]. Given that the peptide binds metal ions, it follows therefrom that it will reduce the formation of ROS as well.

[Note that the two arguments above are not mutually exclusive. That is, it is entirely

possible for the Saitoh peptide to not only bind metal ions, and hence reduce the formation of ROS, but also to promote growth of neuronal tissue].

In view of the foregoing explanation, the claims are rendered obvious.

✧

Claims 1, 9, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §. 103 as being unpatentable over Saitoh (WO 94/09808) in view of Hensley (*Ann N. Y. Acad. Sci.* 786:120-134, 1996) further in view of Zachariou (*Journal of Protein Chemistry* **14**(6), 419-30, 1995).

The explanation provided above (Saitoh in view of Hensley) applies here as well, with the addition that the peptide chemist of ordinary skill would have expected (in view of Zachariou) that the Saitoh peptide will exhibit some affinity for metal ions such as copper and iron owing to the presence of the glutamic acid residue in the peptide.

Thus, the claims are rendered obvious.

✧

Claims 1, 9-11, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Chen, Hua-Ming (*Food Factors for Cancer Prevention, [International Conference on Food Factors: Chemistry and Cancer Prevention*], Hamamatsu, Japan, Dec., 1995 (1997), Meeting Date 1995, 639-641. Editor(s): Ohigashi, Hajime; Publisher: Springer, Tokyo, Japan) or Chen, Hua-Ming (*Journal of*

Agricultural and Food Chemistry **46**(1), 49-53, 1998).

As indicated previously, Chen (1998) discloses (table 1 page 51) that various histidine-containing tripeptides and tetrapeptides inhibit the production of ROS. This is also disclosed on page 640 of Chen (1997). Accordingly, a chemist of ordinary skill would reason that if the production of ROS can be inhibited, the "damage" caused by ROS will be reduced.

In response, applicants have argued that the experiments of Chen were undertaken in vitro, and that one cannot extrapolate from the "test tube" to the intact animal. However, this is the same extrapolation that applicants are proposing. If applicants are permitted to speculate as to effects *in vivo*, then the "artisan of ordinary skill" is free to extrapolate from *in vitro* results, and assume that ROS formation will be inhibited in vivo when the Chen peptide is administered to an animal.

The rejection is maintained.

✧

Claims 1, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Morikawa, Eiharu (*Stroke* (Dallas) **27**(5), 951-956, 1996) or Seko, Yoshinori (*Journal of Pathology* **178**(3), 335-42, 1996).

Morikawa discloses the following peptide (p. 952, col 1, line 2): YTHLVAIQ This peptide is also disclosed in Seko (page 336, col 1, line 6). Both references disclose

that the peptide is effective to treat ischemia. One of ordinary skill would have reasoned that if a peptide is effective to treat ischemia, the "damaging" effects that gave rise to the symptoms of ischemia would be reduced.

Applicants have argued that if a peptide has the sequence YTHLVAIQ, it cannot possibly bind metal ions. However, the metal ion-binding property of any compound is determined by its structure, and applicants cannot prevent such binding by argument alone.

The rejection is maintained.

✧

Claims 1, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Kaplan (*Neuroscience Research Communications* **19**(2), 115-123, 1996).

Kaplan discloses that the following peptide is effective to treat one or more symptoms of ischemia: MEHFPGP

The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of the ischemia.

Applicants have responded by arguing that it is not enough that a reference disclose the

claimed process and the end result that is stipulated in a claim. The reference, according to applicants, must also disclose whatever mechanism of action that the applicant is proposing.

As is evident from the specification, one of the purposes of reducing the formation of, and "damage" by ROS is to mitigate the tissue damage that occurs as a result of ischemia. Accordingly, one embodiment of the claimed method is the following:

> *1003. A method of reducing the damage that occurs as a result of ischemia, comprising the step of administering the following peptide to a subject in need thereof:*
>
> *MEHFPGP*
>
> *1004. The method according to claim 1003 wherein the peptide is able to bind a metal ion.*

Certainly, claim 1003 is rendered obvious by the reference. It appears to be applicants contention, however, that this claim 1004 is not obvious, since the reference does not disclose that the peptide in question is able to bind metal ions. Suppose that there are two physiologists, each conducting experiments on rats. The "first" physiologist induces ischemia in the rat and administers the peptide MEHFPGP. The "first" physiologist subsequently sacrifices the rat, and conducts histological experiments which show that the presence of the peptide reduces the damage to tissues. A "second" physiologist undertakes the same experiments as the first; the "second" physiologist, however, happens to know that the peptide in question binds metal ions, but again,

conducts the experiments exactly as the first physiologist. If applicants were observing the two physiologists, could applicants determine which of the physiologists knew that the peptide binds metal ions, and which physiologist did not? If applicants could not determine any difference between what the "first" physiologist did, and the second, upon what basis are applicants arguing patentable distinction? [(*Ex parte Novitski* (26 USPQ2d 1389, 1993); *Bristol-Myers Squibb v. Ben Venue Laboratories* (58 USPQ2d 1508, 2001); *In re May and Eddy* (197 USPQ 601)].

It is maintained that there is no patentable distinction between the processes conducted by the two physiologists; the rejection is maintained.

✧

Claims 1, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Kaplan (*Neuroscience Research Communications* **19**(2), 115-123, 1996) in view of Zachariou (*Journal of Protein Chemistry* **14**(6), 419-30, 1995).

The explanation given above (rejection over Kaplan) applies here as well, but with the addition that the peptide chemist of ordinary skill would have expected (in view of Zachariou) that the Liotta peptide will exhibit some affinity for metal ions such as copper and iron owing to the presence of the glutamic acid residues in the peptide.

Thus, the claims are rendered obvious.

✧

Claims 1, 3, 9, 11 are rejected under 35 U.S.C. §103 as being unpatentable over Pickart (USP 5,118,665); or Pickart in view of Knight (*Ann Clin Lab Sci* **25**, 111, 1995); or Pickart in view of Roth (*Acta Chirugica Hungarica* **36**, 302, 1997).

As indicated in the first Office action (on the merits), Pickart discloses (e.g., col 18, table 3) that the peptide Gly-Lys-His exhibits SOD activity when complexed to manganese, and further, that the peptide is an antioxidant and can be used to treat inflammatory disorders. Knight discloses that the damage which accompanies inflammation is caused at least in part by "ROS". Roth also discloses that the damage which accompanies inflammation is caused at least in part by "ROS". Thus, it would have been obvious to one of ordinary skill that by administering the peptide Gly-Lys-His (together with manganese) to a mammal, damage caused by ROS can be mitigated.

This rejection was imposed previously, and withdrawn previously. However, upon reconsideration, this rejection is reinstated. The issue concerns the following phrase in the last line of the claim: "or a physiologically-acceptable salt thereof". As recognized by the drug formulation specialist of ordinary skill, there are many metal ions that would qualify as "physiologically-acceptable". Moreover, the specification (page 26, line 19) states that the salt can be a metal ion. Thus, the issue here is one of claim interpretation. According to one interpretation, claim 1 encompasses two separate genera: (a) a method of using a peptide to which a metal ion is not bound, and

(b) a method of using a physiologically-acceptable salt of a peptide. Within this second genus, physiologically-acceptable salts would include metal ions such as copper. Accordingly, the claim can be interpreted to mean that a metal ion is not bound, unless a salt of the peptide is being used, in which case a metal ion can be bound.

One option would be to amend the claim to make clear that, even when a salt of the peptide is being used, no metal ion can be bound.

✧

Claims 1 and 9 are rejected under 35 U.S.C. 103 as being unpatentable over Coy (USP 5,877,277) in view of Malins (*Proc. Natl. Acad Sci.* **93**, 2557, 1996); or Coy in view of Knight (*Ann Clin Lab Sci* **25**, 111, 1995).

Coy discloses (col 22, line 39+; col 22, line 29+) peptides that fall within the scope of instant claim 1. Also disclosed (col 8, line 10+) is that the peptides are effective to treat cancer. Coy does not disclose that tumor cell growth is caused by reactive oxygen species. Malins and Knight both disclose that tumor cell growth is caused at least in part by reactive oxygen species. Neither of Malins and Knight discloses a peptide falling with the scope of instant claim 1.

One of ordinary skill would expect that if cancer is caused by ROS, or if tumor cells give rise to ROS (or if both is true), then eliminating (at least in part) the tumor cells can only take place if the damage caused by the ROS has been mitigated. It may be the case that

Coy does not teach that the disclosed peptides act to directly reduce the formation of ROS. However, given that tumor cells increase the level of ROS, it follows therefrom that if the population of tumor cells is reduced, the amount of ROS produced by the tumor cells will be reduced as well. If the amount of ROS that is produced declines, then it stands to reason that the "damage" caused by those ROS's will also decline.

Thus, the claims are rendered obvious.

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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